UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

No. 2013-1532

CEPHALON, INC. and CIMA LABS, INC.,
Plaintiffs -Appellee,

v.

MYLAN PHARMACEUTICALS INC. and MYLAN INC.,
Defendants-Appellants,

Appeal from the United States District Court for the
District of Delaware in consolidated Case No. 11-CV-0164, Judge Sue L. Robinson.

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November 6, 2013

CERTIFICATE OF INTEREST

Counsel for the appellees, Cephalon, Inc. and CIMA Labs, Inc. certifies the following:

1. The full name of every part or amicus represented by me is:

Cephalon, Inc.
CIMA Labs, Inc.

2. The name of the real party in interest represented by me is:

N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

CIMA Labs, Inc. is a wholly-owned subsidiary of Cephalon, Inc. Cephalon, Inc. is wholly owned by Cupric Holding Co., Inc., which is wholly owned by Teva Pharmaceutical Industries Ltd. No publicly held corporation owns more than 10% of Teva Pharmaceutical Industries Ltd.'s stock.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

Fish & Richardson P.C.: Jonathan E. Singer; Douglas E. McCann, Ahmed J. Davis; John R. Lane; Ellen A. Scordino; Gregory R. Booker; Rebecca L. Shult; Elizabeth M. Flanagan; Michelle Nerozzi-Ankenbrand; David Yaegashi

Date: November 6, 2013

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STATEMENT OF RELATED CASES

This is an appeal from four consolidated cases in the District of Delaware: *Cephalon, Inc. v. Mylan Pharms. Inc.*, No. 11-164 (D. Del.); *Cephalon, Inc. v. Mylan Pharms. Inc.*, No. 11-1111 (D. Del.); *Cephalon, Inc. v. Mylan Pharms. Inc.*, No. 12-73; and *Cephalon, Inc. v. Mylan Pharms. Inc.*, No. 12-247. To the best of Cephalon's knowledge, there are no other currently pending cases in this Court or any other court that will directly affect or be directly affected by this Court's decision in this case.

JURISDICTIONAL STATEMENT

The district court had jurisdiction over these cases under 28 U.S.C. §§ 1331, 1338, 2201, and 2202. On July 22, 2013, the district court issued its Opinion and Order, holding that the asserted claims of the '604, '590, and '158 patents are infringed and that the asserted claims of the '92,832 and '158 patents are valid.[1] [JA00001-63.] On July 23, 2013, the district court entered judgment on those issues. [JA00066.] On August 14, 2013, the district court entered an amended judgment and injunction ordering that the effective date of approval of Mylan's ANDA Products shall be a date no earlier than the latest of the expiration dates of

[1] Before trial, Mylan agreed not to contest infringement of the asserted '92,832 patent claims and dropped its invalidity counterclaims for the '604 and '590 patents.

the ’604, ’590, ’92,832, and ’158 patents. [JA15775-79.] This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether the district court properly found that Cephalon demonstrated by a preponderance of the evidence that the effervescent agents in Mylan's ANDA Products increase fentanyl absorption where Mylan's own data show that effervescence increases absorption, Mylan's scientists stated that effervescence increases absorption, and Cephalon's *in vitro* and *in vivo* data confirm that effervescence contributes to increased absorption?

2. Whether the district court properly found that Cephalon demonstrated by a preponderance of the evidence that the effervescent agents in Mylan's ANDA Products are present in an amount greater than that required for disintegration when Mylan's ANDA Products contain the "optimum" amount of the "superdisintegrant" sodium starch glycolate ("SSG"), Mylan characterized the SSG as a disintegrant to the FDA, and Mylan's data purporting to contradict this function was "unorthodox" and not standard in the industry?

3. Whether the district court properly found that Mylan failed to show by clear and convincing evidence that the asserted claims of the Moe patents are anticipated by the '604 patent where Mylan concedes that the '604 patent fails to disclose expressly the fentanyl doses claimed in the Moe patents, where Mylan improperly attempts to fill the gaps in the disclosure by relying on extrinsic evidence, and where the '604 patent does not disclose the key combination of

elements as arranged in the Moe patent claims?

4. Whether the district court's finding that Mylan failed to show by clear and convincing evidence that any of the asserted claims of the Moe patents are obvious is clearly erroneous where the Moe formulations exhibited an unexpected pharmacokinetic benefit, Mylan's own expert concedes that this benefit was unexpected, and Mylan failed to show any motivation to abandon prior art formulations and turn to the Moe patent formulations?

STATEMENT OF THE CASE

This appeal relates to Fentora®, the only FDA-approved buccal tablet that employs effervescence to speed drug delivery, in this case the powerful opiate fentanyl. Fentora® is indicated for the treatment of breakthrough pain, an agonizing spike of pain that "breaks through" the chronic pain with which cancer patients are already burdened. By using both effervescence and a combination of excipients not known previously to increase drug absorption, CIMA scientists dramatically increased the rate and extent of fentanyl absorption, thereby speeding relief to patients desperately in need.

The first part of this appeal turns on whether Cephalon presented sufficient evidence at trial to demonstrate that the admitted effervescent components of Mylan's copy of Fentora® enhance the absorption of fentanyl, as the Khankari patents require. The evidence at trial demonstrates overwhelmingly that they do. Along with a host of other evidence, Mylan's own development work shows this. In 2008, well before they ever knew litigation would result from their work, Mylan scientists attempted to design around the Khankari patents multiple times but failed, ultimately resorting to copying CIMA's effervescent technology for the precise reason—enhancing absorption—that Mylan now disputes is lacking. Simply stated, effervescence works to enhance absorption and works well, having

a "larger effect on PK than other pH modifiers," as one Mylan scientist later put it. [JA15515.]

As for the Moe patents, Mylan's arguments distort the law of anticipation and obviousness, respectively. On anticipation, Mylan effectively concedes that the alleged anticipatory Khankari '604 patent lacks the required fentanyl dosages, yet asks this Court to incorporate the dosages of a different fentanyl product, Actiq®, "inherently" into that patent. This stretches the law of inherency too far. And, on obviousness, Mylan cannot avoid its own expert's admission that Dr. Moe's formulations with sodium starch glycolate and mannitol were not known, in combination with effervescence, to enhance absorption of fentanyl. Mylan's arguments are hindsight, plain and simple, and, if permitted, would seriously undermine the law of "surprising results," as applied by this Court and the Patent Office to support countless inventions.

In short, Mylan has demonstrated neither "clear error" in fact nor any error in law. The district court's judgment should thus be affirmed.

STATEMENT OF THE FACTS

I. FENTORA®—THE RAPID DELIVERY OF FENTANYL TO TREAT BREAKTHROUGH CANCER PAIN

Many cancer patients suffer persistent pain. Whether caused by the disease itself or as a side effect of chemotherapy, doctors treat this so-called "background" pain with around-the-clock opioid medication. [JA10068-70.]

Cancer patients additionally experience flares of very severe and intense pain called breakthrough pain. [JA10068-69.] These flares generally last for about an hour, and "break through" the around-the-clock medication patients receive to manage their background pain. [JA10069-72; JA10075-76; JA11141-43; JA15789-90.]

Scientists first comprehensively studied breakthrough pain in the early 1990s. [JA10070-72; JA15797-805.] At that time, breakthrough pain treatment options were few: intravenous therapy in the hospital or short-acting oral opioids at home. [JA10072.] Unfortunately, the therapeutic effect of short-acting oral opioids did not adequately match the temporal characteristics of breakthrough pain. Because oral opioids are absorbed across the gastrointestinal tract, it takes time for them to exert a therapeutic effect. By the time that occurs, the pain episode may have already reached its peak. [JA10076-77.] Though not ideal, short-acting oral opioids were at least better than simply increasing around-the-clock opioid medication, which could cause sedation or severe side effects. [JA10074-75.]

In 1998, FDA approved the first oral transmucosal therapy indicated for the treatment of breakthrough pain in opioid-tolerant cancer patients, Actiq®. [JA10073; JA11909.] Anesta Corp., a competitor company to CIMA, developed Actiq®. [JA10708.] The active pharmaceutical ingredient in Actiq®—a lozenge on a stick ("lollipop") formulation—is fentanyl, an exceedingly powerful opioid. [JA11909; JA10073.] Fentanyl is fifty to one hundred times more potent than morphine, and can cause death if any substantial amount is absorbed, even through the skin. [JA10073-75.] Because of this, formulators use as little fentanyl as needed to achieve a desired therapeutic benefit. [JA10069-75; JA10101; JA10914-15.] The largest dose of Actiq®, for example, is 1600 mcg, just 1.6 mg. [JA11910.]

Actiq® offered an improvement over short-acting oral opioids because transmucosal delivery results in faster onset of action. Nonetheless, it had significant drawbacks. [JA10077-79; JA10085-86; JA10915-16.] Chief among these was that patients swallowed substantial portions of the fentanyl in Actiq®, thereby defeating the purpose of transmucosal delivery. [JA11912.]

In 2006, the FDA approved Fentora®, which achieves the clinical benefit of rapid transmucosal delivery without the drawbacks of Actiq®. On top of this, Fentora® provides even faster onset of pain relief than Actiq®, while using a much smaller amount of fentanyl per dose. [JA10086-88; JA10091-92; JA14588-89;

JA15806-12; JA15813-21.] Fentora® achieves these results through the inventions claimed in the Khankari and Moe patents.

II. THE KHANKARI PATENTS—THE DISCOVERY THAT EFFERVESCENCE IMPROVES ORAL TRANSMUCOSAL ABSORPTION

The Khankari patents describe and claim the use of effervescence to increase absorption of drugs across the oral mucosa, in general, and fentanyl, in particular. [JA00105-11; JA00112-18; *see also* JA10184-87.] The oral mucosae are the mucous membranes lining the mouth, and include the buccal, sublingual, and gingival mucosae. [JA10077-78, JA10154; JA10723-24.]

A drug administered by an oral transmucosal route is absorbed across the mucosae and directly into the blood stream. [JA10154-57.] This differs from traditional oral administration where swallowed drug is absorbed across the intestines. [*See* JA10150-58.] Oral transmucosal administration can be beneficial for some drugs, both because direct absorption can be faster and because it avoids degradation of the drug by the liver—the "first pass effect." [JA10157-58; *see also* JA10723; JA10916.] Thus, drugs absorbed through the oral mucosae can achieve greater therapeutic effects with smaller dosages, potentially minimizing side effects. *See also Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1333 (Fed. Cir. 2013).

The concept that effervescence increases oral transmucosal drug absorption originated in the research of inventor Jonathan Eichman in 1995, then a graduate student in the lab of renowned University of Wisconsin professor and inventor Dr. Joseph Robinson. Eichman's research focused primarily on the use of effervescence to increase gastrointestinal absorption, based on a physical effect of bubbling carbon dioxide on the intestinal wall. [JA10158-62.]

Dr. Robinson sat on CIMA's board of directors, and brought Eichman's research concept to Dr. Raj Khankari and CIMA in 1995. [JA10158-62.] Working together, Drs. Khankari and Robinson conceived that, in addition to possible physical effects, the carbon dioxide gas produced by effervescence could also increase oral transmucosal drug absorption through its unique, dynamic effect on the pH of saliva. [JA10162-65; JA10191-92; JA15822-27.]

Dr. Khankari described the dynamic pH effect at trial, just as Mylan's researchers would years later when they developed their ANDA product. [JA10163-67.] An effervescent reaction in the mouth between, for example, citric acid and sodium bicarbonate, first forms carbonic acid in saliva, depressing the pH of saliva and making it more acidic. [*Id*.] Because it is a weak acid, carbonic acid breaks down into water and carbon dioxide, which leaves solution. [JA10163.] As the carbonic acid breaks down, its concentration is reduced, and the salivary pH begins to rise, becoming less acidic and more basic. [JA10163-64.] The

effervescent reaction thus causes a dynamic change in the pH of saliva. [JA10164.] *See generally, Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d at 1334.

This dynamic change in salivary pH is beneficial because it promotes both drug dissolution and absorption, without compromising one in favor of the other. [JA10167.] In order for a drug to be absorbed, it first must dissolve into solution. Acidic pH levels favor dissolution of weakly basic drugs like fentanyl. [JA10162-63; JA10699; JA15831-32.] When weakly basic drugs dissolve, they take on their "ionized" form. But ionized drug forms are not favored for absorption—rather, "unionized" forms are. In turn, basic pH levels favor the unionized form of weakly basic drugs. [JA10162-65.]

Thus, the pH conditions that promote dissolution are often the opposite of those that promote absorption. [*Id.*] In order to convert a weakly basic drug from its dissolved, ionized form to its absorbable, unionized form, the formulator must somehow change from the dissolution-favoring lower pH to the absorption-favoring higher pH. [JA10165.] Dr. Khankari discovered that an effervescent formulation can provide a dynamic change in pH, facilitating ***both*** dissolution and absorption. [JA10163-67; *see also* JA10557-59.] Such a result—optimizing both dissolution and absorption—is "a holy grail for pharmaceutical scientists." [JA10162-63.]

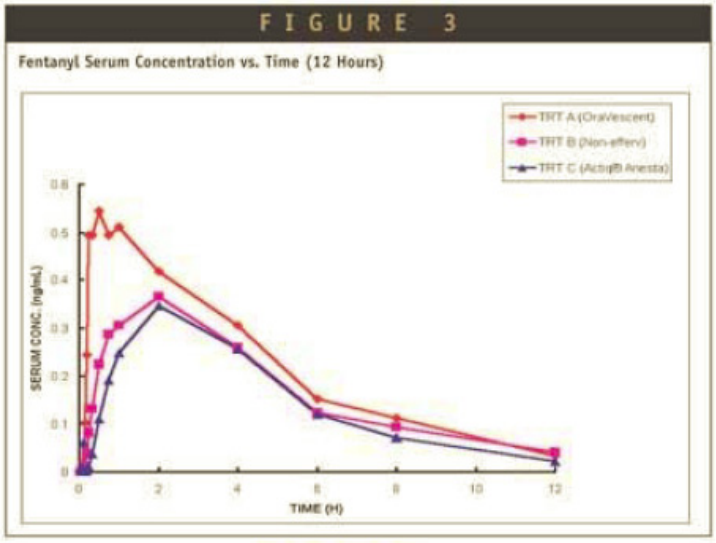
Further development work led to a refinement to the technology: the addition of a pH adjusting substance to the effervescent formulation. [JA10176-78.] Adding a pH adjusting substance, even beyond the effervescent components, offered the advantage of an additional pH boost for absorption (*i.e.*, further adjusting the pH to increase the amount of unionized drug form). [JA10178-79; JA15842; JA15846.]

CIMA named the completed platform technology (*i.e.*, formulations containing both effervescent and additional pH adjusting components) the OraVescent® technology. [JA10179-80.] After choosing fentanyl as its lead candidate, CIMA investigated its prototype OraVescent® fentanyl formulations *in vivo*, first in dogs. The dog study was run by competitor Anesta Corp., the developer of Actiq®. [JA10708.] And while Anesta scientists were unable to isolate non-pH related effects of effervescence, they confirmed the dynamic pH effect: the OraVescent® formulations produced higher fentanyl absorption than both non-effervescent formulations and buffered solutions of fentanyl at elevated pHs. [JA10587-93; JA10705-08; JA10956-58; JA10962-64; JA15876; JA15890; JA15902-04.] Effervescence worked.

CIMA then studied its OraVescent® prototype formulation in its first clinical trial, conducted in Ireland. [JA10180; JA15908-14; JA14773-5208.] The Ireland study compared the OraVescent® prototype formulation with Actiq® and a buccal

tablet lacking both effervescent and pH adjusting components. [JA10180-81; JA15910-11.] The OraVescent® prototype formulation and the non-effervescent formulation had "similar" disintegration times in the Ireland study and approximately the same final pH values. [JA10554-56; JA10938-41; JA15910; JA10695-98; JA15917.]

As depicted in the graph below, the OraVescent® prototype exhibited dramatically better pharmacokinetic or "PK" parameters than the other treatments. [JA15912.] The OraVescent® tablet (red) produced higher overall fentanyl absorption (AUC – a parameter related to the extent of absorption), more quickly reached maximum fentanyl plasma concentration (T_{max}), and achieved a higher maximum fentanyl plasma concentration (C_{max} – a parameter related to the rate and extent of absorption) than both the non-effervescent fentanyl tablet (pink) and Actiq® (purple). [JA10182-83; JA10554-55; JA15912; *see also* JA10616; JA10688-89.]



Ultimately Dr. Khankari and his co-inventors received both the '604 and '590 patents for their CO_2-enhanced oral transmucosal absorption inventions. [JA10184-87; JA00105-11; JA00112-18.] The '604 patent covers the platform technology, whereas the '590 patent specifically relates to fentanyl. In their text, the Khankari patents explain the dynamic pH effect,[2] describing how effervescence and pH adjusting substances work synergistically to promote absorption across the oral mucosae:

> The pH [of] solutions in which an effervescent couple has dissolved is slightly acidic due to the evolution of carbon dioxide. The pH of the local environment, e.g., saliva in immediate contact with the tablet and any drug that may have dissolved from it, may be adjusted by incorporating in the tablet a pH adjusting substances which permit the relative portions of the ionized and unionized forms of the drug to be controlled. In this way, the present dosage forms can be optimized for each specific drug.

[2] The patents also refer to other possible mechanisms by which effervescence may act to increase absorption. [JA00106-07.]

[JA00107; JA10186-87.]

III. THE MOE PATENTS—THE DISCOVERY THAT MANNITOL AND SODIUM STARCH GLYCOLATE UNEXPECTEDLY ENHANCE ABSORPTION OF ORAVESCENT® FENTANYL

With the results of its first clinical study in hand, CIMA took the next steps toward commercializing its OraVescent® fentanyl buccal tablets: large-scale manufacture of the tablets and full blown clinical trials. [JA10184; JA10228-38.] Dr. Derek Moe, CIMA's head of formulation, led a team that modified the OraVescent® prototype formulation to make it commercially viable. [JA10227-28.] After months of work, they arrived at a scaled-up OraVescent® formulation and, in light of the absorption-enhancing effects of effervescence, predicted that a 1080 mcg tablet would be comparable to 1600 mcg Actiq®, a 32.5% fentanyl dose reduction. [JA10235-42; JA14351; JA15924-6140; JA16141-59.] CIMA then conducted two clinical studies (99-09 and 99-10), both of which confirmed that prediction. [JA10242-46; JA11962-67; JA13126-33.]

Soon after receiving these clinical results, however, Dr. Moe and his team experienced an unexpected setback: the scaled-up formulation was unstable. [JA10246-51; JA14355.] The fentanyl in the formulation was "converting into unknown other compounds" called degradants. [JA10247-48.]

Through dozens of studies and the evaluation of numerous additional prototypes, Dr. Moe's team identified a new formulation. [JA10252-64; JA10341;

JA16160; JA14341-43; JA11986.] The new "Moe" formulation employed mannitol and SSG as replacements for lactose monohydrate and crospovidone. [JA10262-65; JA11986.]

Because CIMA had planned to proceed into advanced clinical trials with the same dosing regimen it previously used, Dr. Moe wanted to confirm what CIMA expected would be the case—that the new Moe formulation would produce the same PK profile as that of the scaled-up OraVescent® formulation. [JA10265-68; JA10276-77.] Accordingly, CIMA ran small-scale clinical trials to prove this.

But again, the unexpected occurred—the 1080 mcg Moe formulation tablet was not comparable to 1600 mcg Actiq® anymore. Rather, an even lower dose—the 810 mcg strength Moe formulation—had a C_{max} comparable to 1600 mcg Actiq®. [JA10268-70; JA10276; JA12023.] The results both surprised and frustrated Dr. Moe. [JA10268-69.] On the one hand, the results would allow for a further dose reduction in the amount of effervescent fentanyl that would be comparable to 1600 mcg Actiq®. On the other hand, the results threw a wrench in CIMA's plans to enter costly Phase III clinical trials with the previously chosen dosing regimen. [JA10268-69; JA10276-77.]

Eventually, CIMA proceeded to a Phase III study with the new lower-dose Moe formulation, betting that it would achieve the desired comparability to Actiq® at the even lower doses. [JA10277-81; JA12010-16.] That risky decision proved

correct. A dose proportionality study (99-18) using 810 mcg of the Moe formulation produced high enough C_{max} values to confirm a 50% dose reduction compared to 1600 mcg Actiq®. [JA10281-85; JA15638-50.]

That study also demonstrated another peculiar aspect of the Moe formulation—that it is linear for doses of 810 mcg and below, meaning that a reduction in dose produces a correlating reduction in blood plasma levels—*i.e.*, half as much drug in the tablet will produce half as much drug in the blood. [JA10284-85; JA15638-69.] But above 810 mcg, the formulation is not linear. [JA10285; JA10345-46; JA16162.] Thus, the benefits of the Moe formulation are only realized with doses less than about 800 mcg fentanyl, not higher. [JA10346.]

CIMA filed patent applications on the aspects of the Moe formulation that achieved the surprising PK results described above: fentanyl formulations that include effervescent material, a pH adjusting substance, SSG, and mannitol with fentanyl doses less than about 800 mcg. [JA10287-90.] These applications led to the '92,832 and '158 Moe patents. [JA00119-43; JA00144-69.] The '158 patent explains the unexpected benefits of such formulations:

> It has been discovered that the use of effervescence and/or a pH adjusting substance, and most preferably both, can provide significant advantages particularly in terms of the amount of fentanyl that is required for dosing. It has also been found that certain disintegrants [*i.e.*, SSG] and fillers [*i.e.*, mannitol] in combination with at least one effervescent couple and at least one pH adjusting substance can provide even better, and very unexpected, results.

[JA00154-55; *see also* JA00130; JA10288-90.]

The Moe formulation ultimately became Fentora®, which is commercially available in the 800 mcg strength and lower strengths. [JA10285-85; JA15469.] Fentora® tablets are a commercial embodiment of all of the patents-in-suit. [JA11208.] Fentora® tablets use SSG and mannitol according to the Moe inventions with fentanyl doses below 800 mcg and employ effervescence to improve the delivery of fentanyl across the oral mucosa according to the Khankari inventions. [JA10285-88; JA15469; JA14587; JA14345.] And the dynamic pH shift Mylan so derides is described front and center on the FDA-approved Fentora® label:

> FENTORA® employs the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

[JA14587.]

IV. MYLAN'S ANDA PRODUCTS AND THEIR DEVELOPMENT

Mylan's ANDA Products include 100, 200, 300, 400, 600, and 800 mcg fentanyl buccal tablets. [JA15479; JA16170-71; JA16192.] Each strength has identical ingredients—fentanyl citrate, sodium bicarbonate and citric acid (the effervescent agents), sodium carbonate (the pH modifier), as well as mannitol, sodium starch glycolate, silicon dioxide, and magnesium stearate—and differ only

with respect to the amounts of fentanyl citrate and mannitol. [JA10542; JA15480-83; JA16170-71; JA16192.] Accordingly, Mylan's tablets are nearly identical to Fentora®, except that Mylan's tablets include silicon dioxide and even more of the superdisintegrant SSG (4%) than Fentora® (3%). [JA10543-44; JA16192; JA15469.]

Though in final form they are near copies of Fentora®, Mylan began the development of its tablets in March 2008 with formulations that did not use effervescence. [JA10397-403.] Mylan wanted to design around the Khankari patents by using pH modifiers without effervescence to try to match Fentora®'s enhanced absorption profile. [JA10402-04; JA16207.]

Mylan's development efforts led to three final non-effervescent formulations, each of which contained pH modifiers as well as the superdisintegrant SSG to disintegrate the tablets. [JA10404-05.] None of these non-effervescent formulations enhanced absorption nearly enough to be bioequivalent to Fentora®. [JA10405-423; JA15513.]

Following the failure of the pH-only formulations, Mylan then added effervescence on top of its pH-only design by copying the approach embodied in Fentora®, with citric acid and sodium bicarbonate as effervescent agents and sodium carbonate as a further pH modifier. [JA10423; JA10562-65.] This was a

step that Mylan only reluctantly took, as co-lead formulator Dr. John Twist confirmed:

> Q: If you would have been able to achieve a bioequivalent product without using effervescence, that's certainly the approach you would have taken, correct?
>
> A: Absolutely, yes.

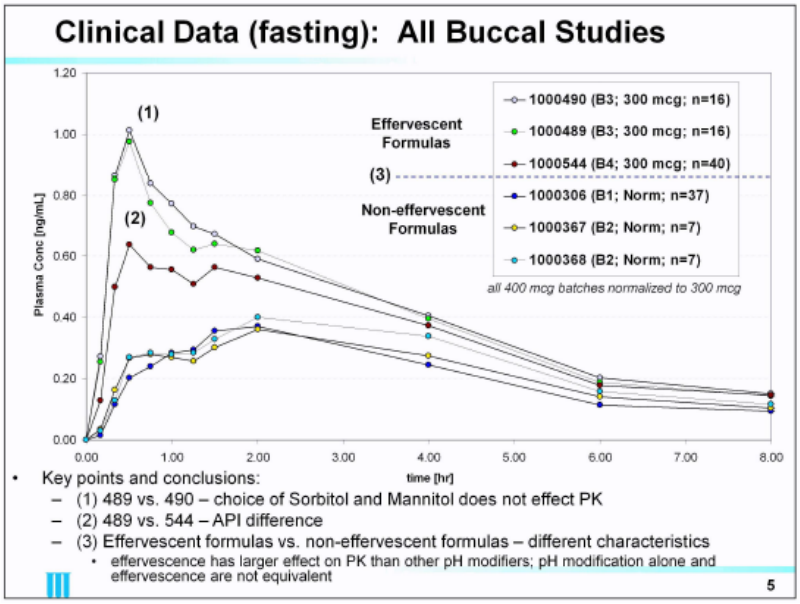
[JA10516.]

In making the switch to effervescence, Mylan learned what CIMA had years before: effervescence is very effective at enhancing transmucosal fentanyl absorption. In fact, Mylan's first two effervescent formulations promoted fentanyl absorption too well; both failed their biostudies for delivering too much drug too fast. [JA10426-29, JA10565-68; JA16218-23; JA16227.] Mylan thus had to offset the enhanced absorption from effervescence by increasing the particle size of fentanyl to reduce its absorption. [JA10428-31; JA10434; JA16260; JA10568-69.] Mylan even considered ***lowering*** the effervescence level to reduce absorption to meet bioequivalency requirements—plainly, Mylan scientists understood that effervescence was improving fentanyl's absorption. [JA10430-31; JA16260.]

Mylan's development work also demonstrated that the improved absorption attributed to effervescence is not—as its lawyers now claim—simply due to improved tablet disintegration. The disintegrant in Mylan's ANDA formulation, SSG, sufficiently disintegrates the tablets *in vivo*. [*See* JA16192.] Notably, SSG is not merely a disintegrant, but is a superdisintegrant, and each formulation Mylan

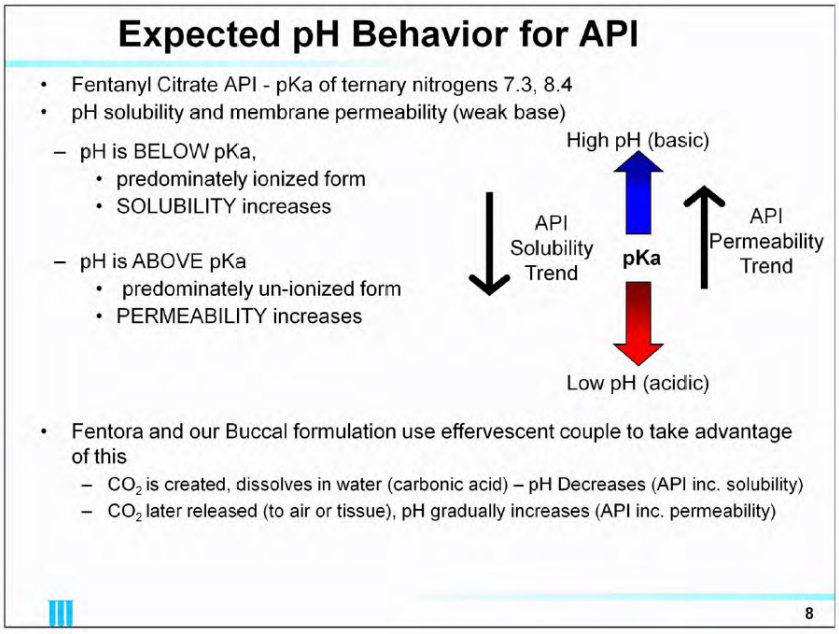
prepared—both effervescent and non-effervescent—contained 4-5% SSG. [JA15513-14.] Mylan formulators regularly used superdisintegrants like SSG to disintegrate tablets in as little as 30 seconds. [JA10384-86; JA10415-16.] Indeed, the trade name of SSG is EXPLOTAB, for the speed with which it works. [JA10265.]

Mylan's scientists not only generated data to show effervescence improves absorption, they analyzed that data for potential use in other projects, as well. In 2011 and 2012, in connection with a new fentanyl project (Abstral®), Mylan scientists reviewed what they had learned about effervescence and created the below slide which shows that in *in vivo* studies, all three of Mylan's effervescent formulations achieve a higher AUC and C_{max}, and reach that C_{max} faster, achieving a higher T_{max}, than Mylan's non-effervescent formulations containing pH modifiers. [JA10435-39; JA15511-95; JA16224-48; JA16267-351.] This led Mylan to conclude as a "key point" that effervescent and non-effervescent formulations have "different characteristics." [JA15515.] Namely, "effervescence has [a] larger effect on PK than other pH modifiers; pH modification alone and effervescence are not equivalent." [JA15515.]



[JA15515; JA10569-71.]

In the same presentation, Mylan's scientists also explained how effervescence improves absorption. As shown below, they believed that the effervescent reaction first helped lower the pH of the solution (aiding fentanyl's dissolution) and then helped slowly raise the pH (increasing fentanyl's absorption). Mylan's conclusion that "Fentora and our Buccal formulation use effervescent couple to take advantage of this [pH-dependent behavior]" was the same as that reached by CIMA scientists in developing Fentora® years before. [JA10489-90; JA15518.]



[JA15518.]

Mylan's scientists' contemporaneous conclusions about the effect of effervescence—that it increases fentanyl's solubility and permeability—speak volumes. Simply put, and in the words of Mylan's lead formulators, "the data" "says" effervescence works. [JA10392.] "[I]t's what is revealed in all these testing." [*Id.*] In none of these presentations do Mylan's scientists say that effervescence is not enhancing absorption or is working only to speed disintegration, as Mylan now so fervently claims. Mylan's scientists know that their ANDA Products infringe the Khankari patents-in-suit.[3]

[3] The reason Mylan's scientists felt so free to make these admissions is that the Khankari patents had been invalidated by the District of Delaware for lack of enablement at the time the statements were made, a decision that was reversed by this Court just a few weeks before trial of this case. *Cephalon, Inc. v. Watson*

V. DISTRICT COURT PROCEEDINGS

The district court held a bench trial from March 4 to March 8, 2013 on the issues of infringement of the '604, '590 and '158 patents, and validity of the '158 and '92,832 patents.[4] On July 22, 2013, the district court issued an opinion ruling in Cephalon's favor. [JA00001-63.]

On infringement of the Khankari patents, the district court addressed the sole claim limitation the parties disputed and concluded that Cephalon had proved that the amount of effervescent agents in Mylan's tablets is both sufficient to increase the rate and/or extent of drug absorption and greater than that required for disintegration. [JA00021; JA00033; JA00038.] As to increased absorption, the district court explained that "[t]he agreed-upon construction requires that the amount of effervescent agent be sufficient to increase the rate and/or extent of absorption" and that this construction "does not preclude the pH-adjusting substance and the effervescent agent from acting synergistically to increase absorption." [JA00024-25.]

The district court then evaluated the evidence of increased absorption presented at trial, finding that all the studies, both *in vivo* and *in vitro*, supported the conclusion that effervescent components in Mylan's tablets increase

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Pharms., Inc., 769 F. Supp. 2d 729, 745 (D. Del. 2011), *rev'd* 707 F.3d 1330 (Fed. Cir. 2013).

[4] Mylan has not appealed the district court's finding of infringement of the '158 patent.

absorption. The district court found that the Anesta dog study supported infringement because it showed that "effervescence, through pH adjustment, at least partially contributed to absorption." [JA00025-27.] The district court further found that the Ireland Study supported Cephalon's position [JA00027-28], as well as the *in vitro* Absorption Systems study Mylan trumpets, which, according to the district court, "support[s] the notion that a combination of effervescence and pH-adjusting substance, identical to that of the ANDA products, improves absorption compared to tablets lacking effervescence and a pH-adjusting substance." [JA00028-31.] As for Mylan's own research, the district court found that even Mylan had concluded "that the combination of effervescent agents and a pH-adjusting substance improved absorption (regardless of why such improvement came about)." [JA00031-32.] Lastly, the district court found that Cephalon had shown that the amount of effervescent agents in Mylan's ANDA Products is greater than that required for tablet disintegration based on the composition of Mylan's tablets, the disintegration behavior of the tablets used in the Ireland Study, and Mylan's own experimental data. [JA00033-38.]

Turning to validity of the Moe patents, the district court first found that the '604 patent does not anticipate the asserted claims of the Moe patents because it does not disclose the claimed fentanyl ranges within its four corners. [JA00045.] The court found that the testimony by Mylan expert Dr. Arthur Kibbe that the

"pharmaceutically effective amount" in the '604 patent discloses fentanyl free base in the range of 100-800 mcg was "conclusive," and not as credible as the testimony of Cephalon's expert, Dr. Lisbeth Illum. [JA00044.] The district court also rejected Mylan's reliance on the Actiq® product as extrinsic evidence of anticipation because Actiq® "is not mentioned in the '604 patent or incorporated therein." [JA00045.]

As to obviousness of the Moe patents, the district court found that the combination of the '604 patent with the Actiq® label and the Handbook of Pharmaceutical Excipients does not render obvious any of the asserted claims of the Moe patents. The district court concluded that Mylan has "not provided sufficient evidence of motivation to use SSG, alone or in combination with mannitol, . . . [and] has not met its burden of showing obviousness." [JA00054.] The district court further found that the "mere identification of SSG as a component known in the art at the time of the invention" does not provide any motivation to "move away from using crospovidone [as in the '604 patent formulation] in favor of using" SSG. [JA00053.]

In concluding the unexpected results favored non-obviousness, the district court rejected Mylan's challenge to the robustness of the evidence. Based on the testimony of Cephalon's expert, Dr. Jerling, the district court found instead that "the unexpected results are sufficiently supported by Cephalon's testing" and are

not disproportionate to the scope of the asserted claims. [JA00055; JA00057.]

Mylan now appeals.

SUMMARY OF ARGUMENT

The district court correctly found that Mylan's ANDA Products infringe the Khankari patents. The district court properly applied its prior claim construction to reach the only reasonable conclusion from the evidence—that Mylan's ANDA Products employ effervescent agents, citric acid and sodium bicarbonate, to increase absorption. This is the same conclusion reached by Mylan's own scientists, and Mylan's assertions of error give short shrift to that evidence, as well as the other evidence from trial, burying most of it in footnotes. That some of that evidence concerns tablets containing both effervescent agents and pH modifiers does not somehow render it irrelevant to prove infringement; rather, each test shows that the effervescent agents in Mylan's tablets contributes to enhanced absorption.

The district court also correctly concluded that Mylan's tablets contain an amount of effervescent agent that is greater than what is required for disintegration. Mylan's tablets contain the same amount of SSG identified in the field as "optimum" for disintegration, and, again, Mylan's own data show that this amount of a superdisintegrant will disintegrate a tablet on its own.

Nor did the district court err in rejecting Mylan's invalidity defenses on the Moe patents. On anticipation, the district court properly found that the '604 patent does not teach the fentanyl ranges recited by the Moe patent claims, and there was

no error in the district court's refusal to go outside the '604 patent to the Actiq® label as urged by Mylan. On obviousness, the district court also properly found that the '604 patent does not render the claims of the Moe patents obvious, including that the data presented that the combination of mannitol and SSG in effervescent formulations further enhances fentanyl absorption demonstrate a surprising and unexpected result.

The district court's judgment should be affirmed.

ARGUMENT

I. STANDARD OF REVIEW

After a bench trial, a district court's factual findings are reviewed for clear error, Fed. R. Civ. P. 52(a)(6), and should be accepted unless this Court is left with the "definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948). An appellate court "may not find facts" in the first instance. *Middleton v. Dep't of Defense*, 185 F.3d 1374, 1383 (Fed. Cir. 1999).

Infringement must be proven by a preponderance of the evidence. *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1317-18 (Fed. Cir. 2000). Infringement is a question of fact. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010).

Invalidity must be proven by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2245-51 (2011). Anticipation is a pure question of fact. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). Obviousness is a question of law based on underlying factual findings. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The "[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998).

II. MYLAN'S ANDA PRODUCTS INFRINGE THE ASSERTED CLAIMS OF THE KHANKARI PATENTS

A. The District Court Correctly Applied Its Prior Claim Construction In Deciding Whether Mylan's Admitted Effervescent Agents Increase Absorption

As found by the district court, all the testing evidence presented at trial demonstrates that the amount of effervescent agents in Mylan's tablets increases fentanyl absorption. Recognizing that the district court's factual findings are not clearly erroneous, Mylan attempts to create a legal error to prevail on appeal. But Mylan cannot challenge the district court's construction of the phrase "at least one effervescent agent in an amount sufficient to increase absorption," because Mylan agreed to it. The only argument Mylan has left is that the district court somehow forgot its own construction and incorrectly applied it in its infringement analysis. But as demonstrated below, the district court understood the scope of the claims in conducting its analysis and correctly found that Mylan infringes.

In the prior *Watson* case, the district court construed the key claim limitation "at least one effervescent agent in an amount sufficient to increase absorption" as follows:

> At least one compound that evolves gas by means of an effervescent reaction is present in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa. This amount is greater than that required for disintegration and does not include the pH-adjusting substance separately claimed.

[JA00021.][5]

This construction requires three things of the effervescent agent beyond the evolution of gas: 1) that it is present in an amount sufficient to increase absorption; 2) that this "amount" must not include the separate pH-adjusting substance; and 3) that the "amount" also is greater than that required for disintegration. Importantly, nowhere in this construction is any particular mechanism of effervescence required, and nowhere does it say that effervescence must increase absorption in isolation from all other components. Rather, the construction simply requires that there be an "amount" of effervescent agent that is, in fact, functioning to increase absorption.

With this agreed-upon construction in hand, the district court summarized the parties' dispute over the absorption requirement as follows: "Cephalon avers that effervescence must enhance absorption, whether by itself or synergistically with another component, while Mylan avers that the effervescence, alone, must enhance absorption." [JA00024.] In accepting Cephalon's position, the district court required proof that the effervescent

[5] While the context of that prior construction is not determinative, it is worth noting that, in that prior case, Cephalon had asserted that one component in the Watson formulation, potassium bicarbonate, was acting as both an effervescent agent and a pH-adjusting substance. *Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d 729, 745 (D. Del. 2011).

agents in Mylan's tablets increase absorption, whether that proof be in the form of studies demonstrating the effect of effervescence on absorption either by itself ***or*** in combination with pH modifiers. [JA00024-25.]

This conclusion by the district court about its own claim construction was proper. As defined, the claim term simply requires that the "amount" of effervescent agent be sufficient to enhance absorption, and that this "amount" cannot include the separate pH modifier. As recognized by the district court, the construction says nothing about ***how*** that "amount" of effervescent agent enhances absorption, whether by itself, or, depending on the drug, in synergy with the pH modifier or some other ingredient in the formulation: "the agreed-upon construction does not require proof of the mechanism or mechanisms by which effervescence increases absorption." [JA00025.]

This conclusion is also consistent with the description of the invention in the Khankari patents' specification. As demonstrated above, that description envisions the use of both effervescent agents and a pH modifier for a weakly basic drug like fentanyl acting together to modify pH, and not in some artificially separate system where one somehow magically works without the other. [JA000107.]

In grafting its additional requirement onto the agreed-upon construction, Mylan selectively quotes the district court's opinion in order to find "error." For example, Mylan quotes a portion of paragraph 47 of the district court's opinion as a supposed example of the district court's "confusion" over its own construction. [*See* Mylan Br. at 6, 29]. According to Mylan, the district court's statement that "the agreed upon construction does not require effervescence to improve absorption independently from pH adjustors" somehow means that the lower court jettisoned the requirement that effervescence enhance absorption. [JA00024.] But all this statement means is that the construction does not preclude effervescence from improving absorption in combination with a pH modifier. And the district court then goes on to say that "[t]he agreed-upon construction does require that the effervescent agent ***function*** to enhance absorption separately and independently from the pH adjusting substance." [JA00025 (emphasis added.)] That is, effervescence must have the function of increasing absorption, and the enhanced absorption, even in a synergistic combination, cannot be solely attributed to the pH modifier.

This is precisely what the district court found in analyzing the evidence—that effervescence increases absorption:

- Cephalon has presented substantial evidence that ***effervescence***, at least in combination with a pH-adjusting substance, increases the rate and/or extent of absorption. [JA00033 (emphasis added).]

- [T]he Ireland study is additional evidence that the ANDA products contain ***effervescent agents*** in an amount sufficient to increase the rate and/or extent of absorption. [JA00028 (emphasis added).]

- [T]he results of the dog study support Cima's argument that citric acid and sodium bicarbonate, ***as effervescent agents***, at least contribute to an enhancement in absorption. [JA00027 (emphasis added).]

The district court applied its construction and found that the effervescent agents in Mylan's tablets in fact increase absorption.

Mylan's argument throughout trial and in its post-trial briefing that Cephalon could not prove infringement without testing a formulation that only had effervescent components (and not a pH modifier) is little more than a straw man. [*See, e.g.*, JA15719-722.] Mylan's formulation has separate effervescent and pH modifying components—the same components as in Fentora® and as used in the Khankari patents (citric acid, sodium bicarbonate and sodium carbonate, respectively)—so, factually, testing formulations with both components was the proper test, as Mylan itself recognized in its own work. And because the district court's claim construction "does not preclude the pH-adjusting substance and the effervescent agent from acting synergistically to increase absorption," there was no error in considering such tests. [JA00025.]

Accordingly, the district court did not, as Mylan claims, ignore its own claim construction or somehow misapply it. Rather, as found by the district court: "Cephalon has presented substantial evidence that effervescence, at least in combination with a pH-adjusting substance, increases the rate and/or extent of absorption. Mylan's argument that Cephalon failed to demonstrate that the ANDA products' effervescence, acting alone, would increase absorption is of no avail under the agreed-upon construction." [JA00033.]

B. The Amount of Effervescent Agents in Mylan's Tablets Increases Fentanyl Absorption

The *in vivo* and *in vitro* data presented at trial demonstrate that the amount of effervescent agents in Mylan's tablets increases oral transmucosal absorption. [*See* JA10553.] Despite all the evidence described at trial and again below, Mylan's retort is that Cephalon did not present what Mylan considers the "right" evidence to prove infringement. According to Mylan, tests comparing tablets containing effervescent agents and pH modifiers to non-effervescent tablets are inadequate to prove infringement under the court's construction. [Mylan Br. at 27.] Mylan's position—grounded in Mylan's lawyers' views that effervescence cannot really work—erroneously overlooks the fact that such comparisons can and do demonstrate that the effervescent agents within those pH-modified tablets enhance absorption.

Mylan's own data generated while developing its ANDA products by itself establishes infringement. In developing its tablets, Mylan first took a non-effervescent, pH modification approach. [JA10404.] Mylan took that approach because it knew fentanyl absorption is pH-dependent, so it thought that identifying the right pH-modification would produce a formulation that achieved the same enhanced absorption as Fentora® but without any effervescent contribution. [*Id.*] Mylan prepared three final formulations that differed in the identity and strength of the pH modifier, but that each contained the same amount of superdisintegrant, 5% SSG. [JA10562-64; JA15513.] But none of Mylan's non-effervescent, pH-modified tablets achieved Fentora®'s enhanced absorption. [JA10404-23; JA10564-65.] Simply put, Mylan's pH-modification approach did not work to enhance fentanyl absorption to the same extent as Fentora®. [JA10561-62; JA16194.]

Once Mylan mimicked Fentora® by using effervescent agents, there was an "enormous change" in the PK profiles of Mylan's tablets. [JA10565-69; *see also* JA10388.] By switching from solely a pH-modification approach to an approach that added effervescence to pH-modification, the absorption profiles of Mylan's tablets skyrocketed. [*See* JA10570-71.] In fact, before its attorneys got involved, Mylan's scientists actually embraced

this result, describing the striking difference on absorption between the effects of its non-effervescent, pH-modified tablets and its copycat tablets employing Fentora®'s OraVescent® technology as follows: "effervescence has [a] larger effect on PK than other pH modifiers; pH modification alone and effervescence ***are not equivalent***." [JA15515 (emphasis added).]

Rather than addressing its own *in vivo* tests, Mylan relegates them to a footnote, blithely claiming they prove nothing because the study tablets contained pH modifiers. [Mylan Br. at 32, n.8.] Even putting aside the attempt to hide this evidence, Mylan's argument ignores that the effects of the pH modifiers are accounted for in its tests because both the non-effervescent tablets and the effervescent tablets contained pH modifiers. [JA10562-63.] The logical conclusion from these tests—reached by everyone but Mylan's counsel—is that it was the effervescence that enhanced absorption. Mylan's current claim that its additional conclusion from these data—that the dynamic pH effect of effervescence accounts for the enhanced absorption property of its ANDA Products—was simply copied from the literature contradicts its internal assessment and, contrary to Mylan's assertion, was not accepted by the district court. [JA00032.] It also strains credulity past the breaking point—that senior scientists at a

sophisticated drug company simply parrot literature in presentations to management about the company's products.

Mylan's scientists meant what they said because it is true. As Dr. Khankari, Dr. Illum and Mylan's co-lead formulator, Ms. Bartley, all described, the dynamic pH effect accompanies an effervescent reaction. [JA10163-67; JA10558-59; JA10389-390.] Mylan's tablets use the effervescent reaction, and thus take advantage of the dynamic pH effect to enhance absorption, just like Fentora®. [JA10557-59; JA16274.] Indeed, Ms. Bartley testifed that she understood that effervescence in Fentora® caused a drop and subsequent rise in pH, and that she believed this drop and rise in pH also occurred with the use of of Mylan's tablets, as the data from Mylan's testing indicate. [JA10389-390; JA10583-84; JA15519.]

Besides Mylan's *in vivo* human data, the district court also found that *in vivo* data from the Anesta dog study "support Cima's argument that citric acid and sodium bicarbonate, as effervescent agents, at least contribute to an enhancement in absorption." [JA00027.] Again, Mylan relegates this evidence to a footnote. [Mylan Br. at 40 n.10.] The Anesta dog study compared tablets containing both effervescent agents and pH modifiers—in the same amounts as in Mylan's tablets—with tablets containing neither, with versions of each formulation that had short and long disintegration

times. [JA14772.] The study also tested a fentanyl solution with a static pH of 7.0, and a fentanyl solution intended to mimic the change in pH observed during dosing of effervescent formulations that had a starting pH of 7.0 and a final pH of 8.0. [JA15881.]

As demonstrated in the graph from the study, the long-disintegrating effervescent formulation (top curve) produced the highest fentanyl absorption as compared to the long-disintegrating non-effervescent formulation (bottom curve) and both pH-modified fentanyl solutions (middle curves). [JA10588-91; JA10705; JA10952-55; JA15890.]

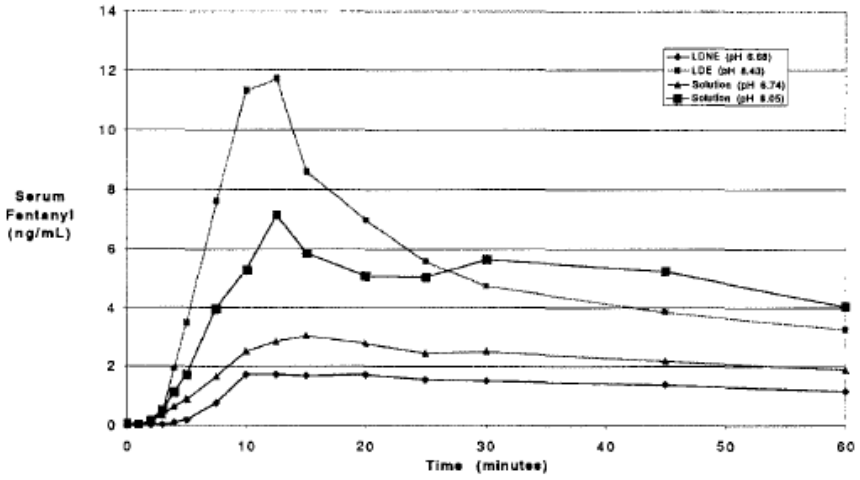


Figure 4. The mean concentration-time profile (n=6) for the formulations administered over 10 minutes.

Similar results were achieved with the short-disintegrating tablets, with the effervescent tablets having greater AUC, a higher C_{max}, and a shorter T_{max} than the non-effervescent tablet. [JA10705; JA10952-55; JA15885-86.]

Accordingly, the effervescent formulations performed best. Rather than address the data in the Anesta dog study and its import, Mylan merely echoes the comments of the study's authors, who, like Mylan, were then competitors of CIMA. [JA10708.] But those comments simply show that the authors were unable, in their opinion, to demonstrate the non-pH effects of effervescence, and not that effervescence has no effect on absorption. In this regard, the aim of the study, according to its authors, was to evaluate the effect of effervescence independent of pH. [JA15876.] Given that pH is the primary mechanism of effervescence's enhanced absorption for fentanyl, the author's conclusions are best understood in that light.

Mylan also wrongly argues in its footnote that, in the Anesta study, effervescent formulations with pH modifiers were only compared to formulations that had neither. [Mylan Br. at 40, n.10.] But the fentanyl solutions in the study had adjusted pH, and did not achieve the same absorption as the effervescent formulations. [JA14743; JA14750.] The enhanced absorption of the effervescent formulations is not a result of a high pH alone because, as CIMA described, higher pH values favor fentanyl absorption but not dissolution, and thus "have a negative influence on the overall dissolution-absorption process. Thus, higher pH alone cannot fully explain the improved absorption of the drug that was seen in this study."

[JA15902.] Instead, effervescence dynamically alters pH, first promoting fentanyl dissolution and thereafter promoting fentanyl absorption. It is simply "erroneous to state that effervescence does not enhance fentanyl permeability when effervescence is the mechanism whereby pH is continually changing." [JA10963-64; JA15903.]

The Ireland study, also relied on by the district court, is further evidence demonstrating that the amount of effervescent agents in Mylan's tablets increases the rate and extent of fentanyl absorption. As demonstrated above, that study shows that a tablet containing the same amount of effervescent agents, 21% sodium bicarbonate and 15% citric acid, and the same amount of pH modifier, 10% sodium carbonate, as Mylan's tablets, produced higher blood levels (C_{max}) and a greater extent of fentanyl absorption (AUC) than a non-effervescent tablet and Actiq®. [JA10554-56; JA15241-42; JA15910; JA15912.] Both the disintegration times and pH of the effervescent and non-effervescent tablets were similar. [JA10556; JA10696-98; JA15908-14; JA15917.] Because the tablets did not disintegrate differently or have different final pH values, the difference in absorption between these tablets is properly attributed to effervescence. [JA10554-56, JA10695-98; JA10938-45; JA15910; JA15917.] The district court thus correctly found that the Ireland study was "evidence that

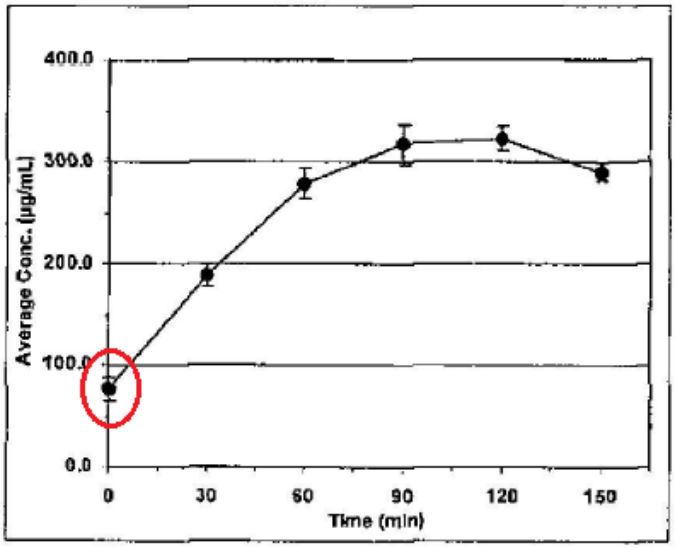
[Mylan's] ANDA products contain effervescent agents in an amount sufficient to increase the rate and/or extent of absorption." [JA00027-28.]

Finally, there is the Absorption Systems report, an *in vitro* study that contains the only data Mylan believes warrant any detailed discussion outside of a footnote. But the district court found that these data supported Cephalon's case, not Mylan's, and Mylan's attempt to assign error to that conclusion improperly re-litigates facts. [JA00028-31.] *Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 702 F.3d 1351, 1358 (Fed. Cir. 2012) ("This court rejects ATC's attempt to retry the case anew on appeal.").

In that study, Cephalon commissioned Absorption Systems to study the absorption of fentanyl across human buccal cells from several fentanyl tablet formulations. The tablets were placed on the surface of buccal cells in the donor chamber and aliquots of buffer were added every minute for four minutes. During the fifth minute the tablets and buffer were mixed. After those first five minutes, samples were taken from the receiver chamber to measure the rate and extent of fentanyl permeability, P_{app}. The first sample taken was assigned the t=0 time point, even though five minutes of the experiment had already elapsed. [JA10708-11.]

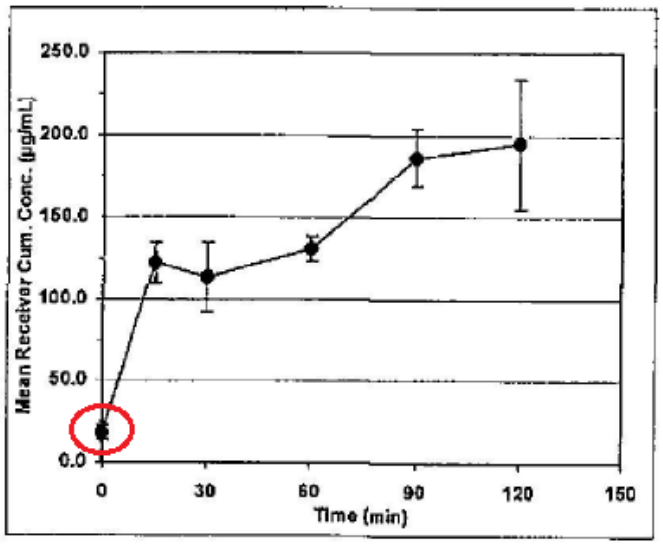
The absorption behavior of tablets containing effervescent agents, both with and without a separate pH modifier, shows that effervescence increases absorption. As demonstrated below, in the first five minutes of the experiment, reflected as t=0 on the graphs, the "effervescent tablet"—which contained both effervescent agents and a pH modifier—and the "no sodium carbonate" tablet—which contained effervescent agents but no pH modifier—both resulted in fentanyl absorption in the first five minutes of the experiment (shown by a concentration of fentanyl above zero at t=0).

Fentanyl dissolved from effervescent 0.8 mg tablet (0.4 mg/mL concentration) (Mean ± STD)



[JA14681.]

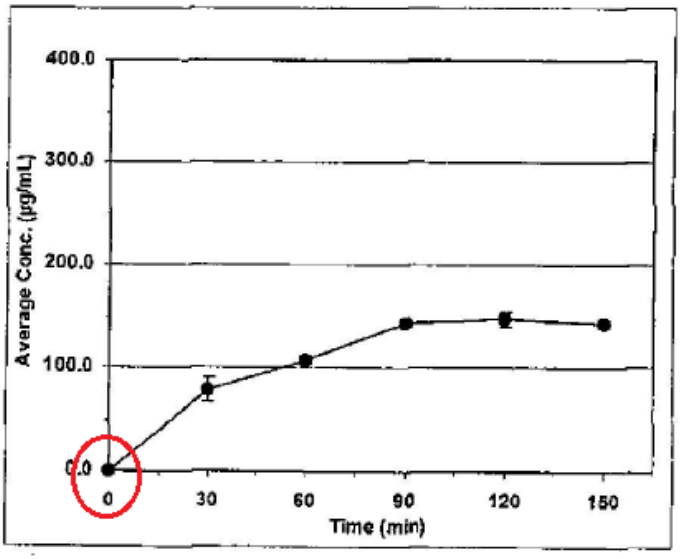
Fentanyl NO Sodium Carbonate dissolved at 0.4 mg/mL concentration (testing on the second cell batch) (Mean ± STD)



[JA14683.]

By contrast, the "noneffervescent" tablet—with neither effervescent agents nor a pH modifier—exhibited no absorption in the first five minutes (shown by a concentration of fentanyl of zero at t=0). [JA10967-971.]

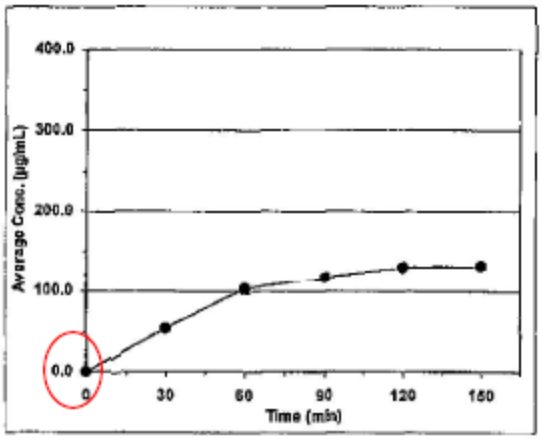
Fentanyl dissolved from noneffervescent 0.8 mg tablet (0.4 mg/mL concentration) (Mean ± STD)



[JA14681.]

In fact, not even a pre-dissolved fentanyl solution (where tablet disintegration cannot be an issue) exhibited absorption in the first five minutes.

Fentanyl powder dissolved at 0.4 mg/mL concentration (Mean ± STD)



[JA14682.]

These data demonstrate that effervescence enhances fentanyl absorption, as the district court found. [JA00031.] The only tablets that showed early absorption in the tests contained effervescent components. And, because all of the tablets were mixed with buffer in the fifth minute of the experiment to disperse the tablets [JA14668], disintegration was a controlled factor in the study. In fact, the effervescent systems outperformed the pre-dissolved fentanyl solution, further demonstrating that effervescence is increasing absorption independent of disintegration. [JA14681-83.]

The Absorption Systems study also highlights the synergies available when effervescence is combined with a pH modifier. In the study, both effervescent and half-effervescent tablets (both of which contain

effervescent agents and a pH modifier) had far greater P_{app} values than the pH only (sodium carbonate only) formulation, showing that combining effervescence and a pH modifier is far better than pH modifier alone, just as Mylan learned. [JA00030; JA10713-14, JA10964-66; JA14674; JA14731.]

C. While Cephalon Need Not Prove the Mechanism(s) By Which Effervescence Increases Absorption, the Evidence Demonstrated that the Dynamic pH Effect Occurs and Contributes to Increased Absorption

As noted, Mylan does not meaningfully address the foregoing evidence in its brief. Instead, Mylan attempts to shift focus away from it and onto whether Cephalon has ever definitively proven a mechanism by which effervescence causes increased absorption. [Mylan Br. at 38-40.] As an initial matter, Cephalon was not required to show how effervescence increases absorption, as the district court properly found. [JA00025; JA00109; JA10759-61; JA10907-08.] *See Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570-71 (Fed. Cir. 1983) (rejecting incorporation of inventor's belief as to how invention worked as a requirement for infringement).

Even so, the weight of the evidence demonstrated that the dynamic pH effect occurs. Drs. Khankari and Illum described it in detail at trial, as do peer-reviewed publications. [JA10163-67; JA10552-53; JA10558-59; JA14633-37; JA15908-10.] Mylan's formulator Tammy Bartley believed

the dynamic pH effect occurred, and Mylan's scientists, after analyzing Mylan's own effervescent data, endorsed the dynamic pH effect as causing enhanced fentanyl absorption. [JA10389-390; JA15518.]

The dynamic pH effect has also been accepted in the medical community. Mylan's own medical expert, Dr. John Loeser, described in his own book dedicated to cancer pain management how "[t]ransient pH changes acompany the effervescent reaction, and increase both the rate of tablet dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl." [JA11298-99; JA11764.] As he testified, he "wrote those words and [he] stand[s] behind them." [JA11299.] And, the FDA, which vigorously monitors drug labeling, permitted Cephalon to describe the effect in its product labeling, which Mylan itself initially copied. [JA10921-31; JA14587; JA16353.]

Mylan's resort to thermodynamics to offer a different rationale for the initial reduced pH—dissolution of citric acid—followed by an increased pH—dissolution of sodium carbonate—is unavailing and at odds with Mylan's scientist's conclusions. [Mylan Br. at 39.] Mylan ignores that the effervescent reaction takes place immediately upon exposure to aqueous solutions, as captured by videos showing the instant evolution of CO_2

bubbles from Mylan's tablets upon exposure to artificial saliva. [JA10372-76; JA10559-60; JA10690; JA16387; JA16388.]

Mylan's further claim that only an "optimum pH range," and not the dynamic control of pH, explains the increased absorption is rife with inconsistencies. [Mylan Br. at 36.] On the one hand, Mylan scientists relied on literature reporting that fentanyl absorption increases as pH increases from 6.6 to 7.7 in selecting a pH-modification only formulation approach. JA10457; JA10639-40; JA16398.] On the other hand, Mylan's lawyers contend that the effervescent systems tested by Absorption Systems, which have pH values below 7 (effervescence, no pH adjustor – pH 6.0; half amount of effervescence + pH adjuster – pH 6.4; and full amount of effervescence + pH adjustor – pH 6.8) have better absorption than non-effervescent tablets at pH 7.0. [JA14731; JA14741.] These theories are irreconcilable, and only serve to demonstrate that the increased absorption is better explained by the dynamic pH effect.

What Mylan is really arguing in debating the merits of the dynamic pH effect is that effervescence does not work to enhance absorption. In essence, Mylan is saying that the Khankari patents are invalid—an argument abandoned by Mylan just before trial, not advanced on appeal, and which is notably at odds with this Court's characterization of the Khankari invention

in the previous *Watson* appeal. The Khankari tablets, this Court explained, "include effervescent agents used as penetration enhancers . . . [t]he Khankari patents also disclose the use of an additional pH adjusting substance in combination with an effervescent agent for promoting the absorption of drugs." *Cephalon*, 707 F.3d at 1333. In describing the dynamic pH effect, this Court stated "[t]he effervescent reaction occurring in the mouth affects the pH level of the saliva . . . when carbon dioxide dissolves in saliva, it forms a weak acid (carbonic acid) that reduces saliva pH . . . the carbon dioxide is released as gas, causing the pH to slowly rise providing for the initial low pH level suitable for dissolution and the eventual high pH level ideal for absorption." *Id.* at 1334. This Court's previous characterization of the effervescent effect was correct. Effervescence—just as Mylan itself demonstrated in preparing its ANDA formulation—increases absorption.

D. Mylan's ANDA Products Contain an Amount of Effervescent Agent Greater than that Required for Disintegration

Despite the evidence presented at trial that the amount of effervescent agents in Mylan's tablets increases fentanyl absorption, Mylan claims that effervescence does no more than disintegrate its tablets. But all the evidence presented at trial demonstrates otherwise, as the district court concluded in determining Mylan's infringement. [JA00037-38.]

The Handbook of Pharmaceutical Excipients identifies the precise amount of SSG in Mylan's tablets, 4%, as the "optimum" concentration of that disintegrant to include in tablets. [JA11955; JA10997; JA16192.] The Handbook states that SSG "is widely used in oral pharmaceuticals as a disintegrant . . . . The usual concentration employed in a formulation is between 2-8%, with the optimum concentration about 4% although in many cases 2% is sufficient." [JA11955.] The "optimum" concentration of SSG generally identified by the Handbook and contained in Mylan's tablets is sufficient to disintegrate Mylan's tablets. [JA00033-34; JA10571-72, JA10578.]

Mylan's characterization to FDA that SSG is the disintegrant in its ANDA Products is additional evidence that the amount of effervescent agent in its tablets is greater than required for disintegration. [JA00034; JA16192; JA16194.] Mylan's characterization is unsurprising. Mylan knows from prior experience that superdisintegrants like SSG will disintegrate non-effervescent tablets within 30 seconds upon being placed in the mouth. [JA10384-86; JA10415-16.]

That Cephalon's NDA characterizes the sodium bicarbonate and citric acid in Fentora® as effervescent components that have disintegration properties does not mean that effervescence is required for disintegration.

[Mylan Br. at 42.] Indeed, the Khankari patents recognize that a separate disintegrant may be preferably incorporated in a formulation, and also that effervescent agents may facilitate disintegration while also acting separately to increase absorption. [JA00106-08; JA00114-16; *see also* JA10695; JA16405.] And, just like Mylan, Cephalon identified SSG as the "disintegrant" in the Fentora® tablets. [JA14346.]

Indeed, Mylan's own scientists did not think to use effervescent agents in their formulation for any purpose other than to modify pH. [JA10506-07.] They did not incorporate effervescent agents into the formulation to facilitate disintegration, as Mylan now claims is their sole function, but rather to achieve enhanced absorption, as described above and illustrated in Mylan's own presentations.

The Ireland study provides additional evidence that the 4% SSG in Mylan's tablets is sufficient for disintegration, as the district court found. [JA00034.] The effervescent and non-effervescent OraVescent® prototypes studied in Ireland both contained 3% crospovidone, which, like SSG, is a superdisintegrant. [JA10385-86; JA10938-40; JA15696-97.] The OraVescent® prototype contained the same percentages by weight of effervescent agents and pH modifier as Mylan's ANDA Products. [JA15696-97; JA16192.] The effervescent and non-effervescent Khankari

prototype tablets had "similar disintegration times," demonstrating that 3% by weight of a superdisintegrant alone sufficiently disintegrated the tablets without any effervescent "assistance," as even Mylan's expert, Dr. Weiner, admitted. [JA15910; JA10940-41.] In other words, no amount of effervescent agent is ***required*** to disintegrate a tablet that already contains enough superdisintegrant for disintegration. This is true both of the OraVescent® prototype tablets, Fentora®, and Mylan's ANDA Products.

While burying its own absorption data in a footnote, Mylan does discuss "above the line" some of its own testing data on disintegration. In the main, Mylan relies on *in vitro* disintegration "screen" tests as evidence that effervescent Fentora® tablets rapidly disintegrate, but that non-effervescent tablets containing 5% SSG do not. Those screen tests involved placing a tablet on top of a screen and then submerging a minor portion of the tablet in water for twenty minutes. [JA10478-480; JA15504.] The screen test is not standard in the industry by any means. Rather, it was created by Mylan scientists; one of whom, Dr. Wargo, referred to the test as "unorthodox" at trial. [JA10478.] The district court concluded that the screen test "does not reliably mimic *in vivo* disintegration," and found it deserving of "little weight." [JA00037.] That is exactly what Cephalon's

expert, Dr. Illum, concluded upon reviewing those tests. [JA10576-77; JA10687-88.]

Mylan also unsuccessfully reargues the import of its *in vivo* disintegration testing comparing Fentora® tablets to some of Mylan's non-effervescent tablets. Here, Mylan errs because, with the exception of lot 1000306, the disintegration data were incomplete. [JA10683-84; JA16340.] The tests stopped after 30 minutes and therefore did not indicate whether the tablets would have disintegrated had the test continued. Accordingly, the district court did not consider such tests, which were not "particularly helpful," because they "placed an artificial temporal limitation on disintegration . . . ." [JA00037.] Moreover, as Mylan well knows, its tablets contained insoluble excipients that will not completely dissolve (5% SSG; 0.8% silicon dioxide; and 0.5% magnesium stearate), leaving remnants in the mouth even after disintegration is complete. [JA10493.] Thus, complete tablet disintegration does not equal complete tablet disappearance. [JA10682-83.]

But, even so, Mylan ignores much of its *in vivo* disintegration data. As demonstrated at trial, one of Mylan's non-effervescent tablet formulation containing 5% SSG (lot 1000306), and effervescent Fentora® tablets containing 3% SSG comparably disintegrated. [JA00037; JA10573-75.] On

average, Mylan's non-effervescent tablets from this lot disintegrated in 27.5 minutes and effervescent Fentora® tablets disintegrated in 24.2 minutes. [JA16340.] These data demonstrate that non-effervescent and effervescent tablets containing SSG in the ranges recommended by the Handbook behave similarly *in vivo*. [JA10573-75; JA16340.]

The district court's assignment of little or no weight to Mylan's disintegration data collected on an artificial timeframe does not constitute legal error, either. The agreed upon construction does ***not*** impose temporal limitations on disintegration. [JA00037.] Mylan cannot now rewrite on appeal the claim construction it expressly agreed to by importing an artificial and unsupported time limit within which tablet disintegration must occur.

Lastly, although the district court's factual findings were based on circumstantial evidence, that evidence is not "any less credible or persuasive" than direct evidence. *Alco Standard Corp. v. Tenn. Valley Authority*, 808 F.2d 1490, 1503 (Fed. Cir. 1986). Indeed, "[c]ircumstantial evidence [of infringement] is not only sufficient, but may also be more certain, satisfying and persuasive, than direct evidence." *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1272 (Fed. Cir. 1986) (quotation omitted). And while Mylan faults Cephalon for not conducting a set of tests it now suggests would be dispositive of the disintegration issue,

Cephalon is under no obligation to do so. *See Martek Bioscis. Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) ("A patentee may prove infringement by 'any method of analysis that is probative of the fact of infringement.'") (internal citation omitted). The facts show that 4% SSG sufficiently disintegrates Mylan's tablets, and the district court did not factually or legally err in making that determination.

III. THE DISTRICT COURT PROPERLY REJECTED MYLAN'S INVALIDITY DEFENSES TO THE MOE PATENTS

A. The '604 Patent Does Not Anticipate the Asserted Moe Patent Claims

1. The '604 Patent Does Not Expressly or Inherently Disclose the Fentanyl Ranges Claimed in the Moe Patents

The asserted claims of the Moe patents require specific amounts of fentanyl: about 100 mcg to about 800 mcg, calculated as fentanyl free base. As the district court found, "the '604 patent does not disclose [these] claimed amounts of fentanyl." [JA00044.] In fact, the '604 patent mentions fentanyl in only one place, Example 1, which describes two effervescent fentanyl dosage forms each containing about 1000 mcg of fentanyl free base. [JA00108; JA11069-70.] That amount of fentanyl exceeds the highest amount of fentanyl (800 mcg) claimed in the Moe patents. [JA11072.] The '604 patent thus cannot expressly anticipate the asserted claims, as the district court concluded. [JA00044.]

Nor does the '604 patent inherently disclose the claimed Moe fentanyl dosages through its use of the phrase "pharmaceutically effective amount" in relation to the amount of drug that should be used with the effervescent technology. Notably, the '604 patent uses the asserted phrase solely in the claims, which do not claim fentanyl, but instead are more general. [JA00105-11.] Mylan thus must argue that by referencing fentanyl as a drug that can be used with effervescence elsewhere in the '604 patent, any amount of fentanyl that might be pharmaceutically effective in that technology is inherently disclosed along with it.

This does not meet the standard of inherency, which requires that the missing subject matter necessarily be present. *Trintec Indus. Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002). While 800 mcg was known as a dosage of fentanyl in other products, specifically Actiq®, the bare reference to "pharmaceutically effective amount" does not incorporate those doses into the '604 patent. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). That phraseology cannot inherently disclose the 800 mcg and lower dosages found in the Moe claims.

In tacit recognition of this, the Actiq® argument was not even advanced by Mylan at trial. Rather, Mylan's expert claimed that another patent incorporated by reference into the '604 patent explained "pharmaceutically effective amount," but upon cross examination conceded that that other patent had nothing to do with

fentanyl. [JA11073-75.] Accordingly, after trial Mylan lifted its arguments about the Actiq® label from its obviousness defense to make out this new anticipation defense.

As the district court recognized, however, Mylan's use of the Actiq® disclosure is improper gap filling at best. [JA00045-46.] As this Court has explained, extrinsic evidence like the Actiq® label "is necessarily of limited scope and probative value" to the anticipation inquiry. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), *overruled on other grounds by Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). This "limited" role is to educate the decision-maker as to what a reference meant to persons of ordinary skill in the art at the time of the invention, and "not to fill gaps in the reference." *Id.*

Yet, filling gaps in the '604 patent with the Actiq® disclosure is exactly what Mylan is doing. Actiq® is not even mentioned in the '604 patent. [JA00045.] Nor has Mylan identified any reason why a skilled artisan would turn to knowledge of Actiq®—a non-effervescent fentanyl lozenge—to explain the "pharmaceutically effective amount" language of the '604 patent, which is directed to the use of effervescence. [JA00105-11.] In this regard, rejecting Mylan's reliance on "pharmaceutically effective amounts" of the different Actiq® dosage form does not mean, as Mylan argues, that the use of the phrase "pharmaceutically

effective amount" can never anticipate a claimed numerical range. It means only that, under the circumstances here, the phrase does not anticipate the claimed numerical range.

Mylan's arguments highlight its continued conflation of the principles of anticipation and obviousness. According to Mylan, the district court acknowledged that a person of ordinary skill in the art would understand a "pharmaceutically effective amount" of fentanyl to include 200-800 mcg fentanyl based on the disclosure of Actiq®. But Mylan derives support for this argument by drawing from two primary sources: Dr. Kibbe's obviousness testimony [JA11003-06; JA11022-24; JA11101], which was not accepted, and the district court's obviousness analysis regarding the disclosure of the '604 patent ***combined with*** the disclosure of Actiq®. [JA00049.] This has nothing to do with anticipation. Instead, the district court saw Mylan's argument for what it was, and correctly found "[t]o the extent Mylan relies on the Actiq® brochure for the disclosure of the fentanyl ranges, its argument relates to obviousness, not anticipation, because the Actiq® brochure is a separate reference." [JA00045-46.] *Scripps*, 927 F.2d at 1577 ("If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not § 102 anticipation, but § 103 obviousness.").

Moreover, the district court found the testimony of Dr. Kibbe, Mylan's expert, "conclusive" which, in fact, it was. [JA00044.] Conclusive expert testimony is not clear and convincing evidence of patent invalidity. *See, e.g.*, *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1338 (Fed. Cir. 2013) (rejecting expert's testimony regarding lack of enablement because *ipse dixit* statements "cannot be enough to constitute clear and convincing evidence"); *Koito Mfg. Co., Ltd. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1152 (Fed. Cir. 2004).

The district court also credited Cephalon's expert, Dr. Illum, over Dr. Kibbe, on this issue. [JA00044.] This Court has stated that "[c]redibility determinations by the trial judge can virtually never be clear error." *Agfa Corp. v. Creo Prods. Inc.*, 451 F.3d 1366, 1379 (Fed. Cir. 2006); *see Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination."). The district court's findings on the missing fentanyl dosages from the Khankari '604 patent should be affirmed.

2. The '604 Patent Does Not Disclose the Combination of Ingredients as Arranged in the Asserted Claims of the Moe Patents

In addition to failing to disclose the fentanyl concentrations of the Moe patents, the '604 patent also fails to disclose the key combination of ingredients—fentanyl, effervescence, SSG, and mannitol—that produced the unexpected

enhanced absorption, as arranged in the Moe claims. Each of the asserted Moe claims are directed to effervescent fentanyl formulations with mannitol in an amount of about 10% to about 80% by weight and SSG in an amount of about 0.25% to about 20% by weight (with the exception of claim 3 of the '92,832 patent, which requires about 0.5% to about 10%). [JA00119-43; JA00144-69.]

The '604 patent discloses four formulations (Examples 1 and 2), none of which include the combination of fentanyl, mannitol, and SSG (or fentanyl, mannitol, SSG and no crospovidone). [JA00108; JA11080.] In fact, none of the four formulations include SSG, nor do any include mannitol and fentanyl with effervescence. Rather, the two fentanyl formulations (Example 1) include lactose (not mannitol) as a filler. [JA00108.] And the short-disintegration time tablet includes microcrystalline cellulose and crospovidone (not SSG) as disintegrants. [JA00108; JA11075-76.] Thus, the '604 patent examples teach one of ordinary skill in the art to use crospovidone (which is specifically disclaimed in the '92,832 patent) as a disintegrant in an effervescent fentanyl formulation. The long-disintegration time fentanyl tablet does not include a disintegrant. The two perchlorperazine formulations (Example 2) include mannitol as a filler, but do not include fentanyl or SSG. [JA00108.]

Mylan cannot point to any specific disclosure in the '604 patent of tablets having, or even a preference for tablets having, the precise compositions of the

asserted Moe patent claims as arranged in those claim, which is required for a prior art reference to anticipate. This is because the precise arrangement of fentanyl (in the 100 mcg to 800 mcg range), mannitol, and SSG, in all asserted claims of the Moe patents, and fentanyl (in the 100 mcg to 800 mcg range) mannitol, SSG, and no crospovidone, in claim 4 of the '92,832 patent is found nowhere in the '604 patent.

Mylan does not contend otherwise. Instead, Mylan argues that because the district court found that the '604 patent discloses the use of mannitol as a "suitable" filler in effervescent formulations and, separately, SSG in a "short[] list" of disintegrants for effervescent formulations, the district court's finding necessitates a finding that the combinations as claimed in the Moe patents are anticipated. [JA00043.] Mylan is wrong. While the district court made these findings, it did not find that the '604 patent taught the ***combination*** of mannitol and SSG in an effervescent ***fentanyl*** formulation. [JA00043.] "Because the hallmark of anticipation is prior invention," to anticipate, a prior art reference must disclose all elements of the claim "***arranged or combined in the same way as in the claim***." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369-70 (Fed. Cir. 2008) (emphasis added). Mylan's failure to show that the '604 patent discloses all of the limitations recited in the asserted claims of the Moe patents arranged or combined in the same way as in those claims is fatal to its anticipation argument.

Id. (reversing district court's grant of summary judgment that patent claim was invalid as anticipated because it is not enough that all of the limitations of the claim could be found in the prior art reference).

William Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356 (Fed. Cir. 2012) does not teach otherwise. *Wrigley* acknowledges that a prior art reference cannot anticipate unless it discloses "all of the limitations of the claim, 'arranged or combined in the same way as in the claim.'" *Id.* at 1361 (quoting *Net MoneyIN*, 545 F.3d at 1370). Mylan's reliance on *Wrigley* fails for this reason alone.

Mylan also erroneously attempts to draw parallels to *Wrigley* because in that case, as here, the prior art patent provided categories of ingredients. [Mylan Br. at 51.] In *Wrigley*, the asserted claim at issue covered a chewing gum composition that consisted of a coolant and flavoring agent, each present in certain ranges. *Id.* at 1359. It was undisputed that the anticipatory prior art reference specifically disclosed the flavoring agent and coolant to be used in chewing gum. *Id.* at 1361. Here, in contrast, the '604 patent does not disclose fentanyl within the 100 to 800 mcg ranges claimed in the Moe patents, so it cannot disclose the combination of mannitol and SSG with the required fentanyl doses. Accordingly, *Wrigley* is inapposite here, and the claims are not anticipated for this additional reason.

B. The '604 Patent Does Not Render Obvious the Asserted Moe Patent Claims

1. The Combination of SSG and Mannitol to Enhance Absorption in Effervescent Fentanyl Formulations Was Unknown in the Art

The district court also properly found that Mylan failed to show by clear and convincing evidence that the '604 patent renders the asserted claims of the Moe patents obvious. Mylan's obviousness defense is classic hindsight. The Moe patents describe an existing problem in the art—lowering the dose of fentanyl (a potent opioid) in an effervescent tablet formulation, while maintaining similar efficacy to the existing Actiq® product. [JA00126-27; JA00151-52; JA11190-91; JA11202-03.] As the Moe patent specifications explain—immediately after discussing the '604 patent—"[i]f lower doses of fentanyl which nonetheless provide similar pain relief could be achieved, patients could obtain comparable benefit with much less drug at lower cost and with a reduced risk of side effects. Thus, improvement in the administration of fentanyl is still desirable." [JA00126; JA00151.] By combining SSG and mannitol with effervescence, Dr. Moe was able to achieve comparable fentanyl blood levels with a fifty percent reduction in fentanyl compared to Actiq®, and a significant reduction from 1080 mcg to 800 mcg compared to the effervescent formulations described in Example 1 of the '604 patent. [JA00126-27; JA00151-52; JA10270; JA10275-77; JA11202-03; JA11218-19.]

Using mannitol and SSG in an effervescent fentanyl formulation to achieve similar efficacy with a lower dose of fentanyl is disclosed nowhere in the '604 patent. Mylan's expert, Dr. Kibbe, confirmed its absence from the prior art. [JA11082.] Dr. Kibbe also agreed that he would not expect any pharmacokinetic benefit from the use of mannitol and SSG instead of lactose and crospovidone (as disclosed in Example 1) in an effervescent fentanyl formulation. [*Id.*; JA00053.] This testimony was not lost on, or confused by, the district court as Mylan contends. [*See* JA00051-53.] As the court explained "Dr. Kibbe opined that the use of mannitol and SSG instead of lactose and crospovidone would not have been expected to benefit the PK characteristics of a formulation." [JA00053.]

In its brief, Mylan does not seriously dispute that the Moe formulation resulted in higher PK values, and that this result was unexpected. This concession is fatal to Mylan's obviousness attack. In light of the problem in the art—delivering lower, yet effective, levels of fentanyl—Mylan has not established there was "a finite number of identified, predictable solutions." *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). And Mylan's own expert conceded that he would not have expected the combination of mannitol and SSG to provide enhanced fentanyl absorption. [JA00053; JA11082.] Thus, the Moe inventions would not have been obvious to one of ordinary skill in the art. *Leo Pharm. Prods., Ltd., v. REA*, 726 F.3d 1346, 1357 (Fed. Cir. 2013).

At trial, Mylan could point to no motivation for Dr. Moe, or any person of ordinary skill in the art, to abandon the use of lactose and crospovidone (Example 1 of the '604 patent), in favor of mannitol and SSG in oral transmucosal fentanyl tablets. [JA00053.] Instead, Mylan identified a different problem as providing the motivation—an argument that it attempts to run away from on appeal. Mylan argued that a person of ordinary skill in the art would have been motivated to modify the formulation of Example 1 of the '604 patent into the formulations claimed in the Moe patents to overcome unexpected stability issues observed in CIMA's internal and confidential accelerated stability testing on its scaled-up version of that formulation. [JA11027; JA11090-91; JA16657-62.] But, as the district court correctly found, Mylan could not rely on the problems that the inventors unexpectedly encountered in non-public development work to support a conclusion of obviousness. [JA00051-52; *see* JA10232-37; JA10246; JA10250-52.] *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight.").

On appeal, Mylan does not point to any motivation to abandon lactose and crospovidone in favor of mannitol and SSG. Instead, Mylan asks this Court to find that the mere disclosure of mannitol (as a filler) and SSG (as a disintegrant) on non-limiting lists of excipients in the '604 patent renders obvious the formulations

claimed in the Moe patents. But again, Mylan cannot establish that the combination of mannitol and SSG was an "identified, predictable solution" to the problem of providing lower, yet effective, levels of fentanyl. *KSR*, 550 U.S. at 421.

Taking Mylan's argument to its logical conclusion, any patent that discloses lists of excipients would invalidate as obvious every claim directed to a drug formulation containing excipients identified in the lists. The mere identification of a potential excipient, however, is not a reason to use that excipient. *Id.* at 418 ("[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.") Mylan has improperly "collaps[ed] the obviousness analysis into a hindsight-guided combination of elements" to construct a reason why a skilled artisan would have selected a different disintegrant and filler than those employed in the short-disintegration time formula of the '604 patent's Example 1. *Leo Pharm.*, 726 F.3d at 1354.

2. The Surprising Results Are Reasonably Commensurate with the Scope of the Claims

The unexpected results in this case are striking. So striking that Mylan's own expert, Dr. Kibbe, admitted them. [JA11082.] This objective indicia of non-obviousness highlights Mylan's hindsight colored obviousness analysis. As this Court recently reconfirmed, "consideration of the objective indicia is a part of the

whole obviousness analysis, not just an afterthought." *Leo Pharm.*, 726 F.3d at 1357. Indeed, objective indicia evidence "can be the most probative evidence of non-obviousness in the record, and enables the . . . court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (citation omitted).

On appeal, Mylan does not seriously quarrel with the district court's findings on this issue. This is because the district court correctly concluded that the formulations claimed in the Moe patents resulted in pharmacokinetic benefits that were "unexpectedly better" than the formulations disclosed in the '604 patent. [JA00056.] At trial, Cephalon's expert Dr. Jerling testified about the data he analyzed from two studies on the OraVescent® formulation described in the '604 patent (Study Nos. 099-09 and 099-10) and two studies on the formulations claimed in the Moe patents (Study Nos. 099-11 and 099-18). [JA11133-34; JA11962-85; JA12017-3125; JA13126-4295; JA15638-69.] All four studies collected the same pharmacokinetic data. [JA11134.] Study Nos. 099-10 and 099-11, where subjects received a 1600 mcg Actiq® dose as an "active control," allowed Dr. Jerling to reliably compare the pharmacokinetic data of the '604 patent formulation to the Moe formulation. [JA11139-40; JA11146-48; JA16703.]

Dr. Jerling's analysis demonstrated that the Moe formulation resulted in pharmacokinetic values for C_{max} and AUC that were each about 30% higher than

the same values for the '604 patent formulation, and that the differences in the values were statistically significant at the 5% significance level. [JA11147-48; JA11152-53; JA16704-06.] For an 810 mcg dose of the two different formulations, the average concentration of fentanyl in the blood after 1 hour—a critical time period for breakthrough pain—was higher for the Moe formulation at a 0.001 significance level, meaning that the likelihood that this higher value would have happened by chance is less than one in one thousand. [JA11154-55.]

The only challenge Mylan raises to these results is questioning whether the district court's finding that the unexpected results obtained and, ultimately, patented through the claims to the formulation that achieved them, are not sufficiently commensurate in scope with the claims. [JA00057.] But objective indicia of nonobviousness "need only be 'reasonably commensurate with the scope of the claims.'" *Rambus, Inc. v. Rea*, --- F.3d ---, 2013 WL 5312505, at *8 (Fed. Cir. Sept. 14, 2013); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1309 (Fed. Cir. 2011) ("[A] rigid requirement of absolute identity that ignores relevant properties of claimed compounds would defy the mandate of § 103 requiring consideration of the claimed 'subject matter as a whole.'").

As discussed above, the effervescent fentanyl formulation with 3% SSG and 47-49% mannitol unexpectedly enhanced transmucosal fentanyl absorption. While the claimed ranges are broader, skilled artisans consider these ranges to be typical

and reasonable ranges of mannitol and SSG employed in tablet formulations. [JA10343-44; JA11209-10.] *In re Kollman*, 595 F.2d 48, 56 (CCPA 1979) ("[T]he unobviousness of a broader claimed range can . . . be proven by a narrower range of data" when a person of ordinary skill in the art can ascertain a trend in the exemplified data that "would allow him to reasonably extend the probative value thereof."). Dr. Kibbe testified that mannitol is widely used in pharmaceutical formulations and preparations in the amount of 10-90%, and the Handbook of Pharmaceutical Excipients discloses that 10-90% w/w mannitol is typically used in tablet formulations.[6] [JA11030-31; JA11949.] The Handbook also discloses that 2-8% SSG are typical concentrations used in tablet formulations, and Dr. Illum explained that the full claimed range of 0.5-20% w/w is reasonable for a disintegrant like SSG. [JA11209-10;JA11955.] Both Dr. Kibbe's and Dr. Illum's testimony provide "an adequate basis to support the conclusion that other embodiments falling within the [Moe] claim[s] will behave in the same manner," and establish that the unexpected results are commensurate with the scope of the claims. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

[6] On appeal, Mylan asserts that it offered testimony showing that the data do not support finding unexpected results at other percentage concentrations. [Mylan Br. at 59.] Putting aside the fact that the district court found this assertion to be "based solely on attorney argument [JA00057], Mylan's cited testimony is conclusive and contradicts Dr. Kibbe's testimony that mannitol is commonly used in ranges of 10-90%, as well as the Handbook's disclosure of the typical ranges of mannitol and SSG.

Mylan's reliance on *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003) and *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005), is misplaced. In both *Peterson* and *Harris*, the patentees' claims were directed to a narrow range of components that overlapped with ranges of those same components disclosed in the prior art. *See Peterson*, 315 F.3d at 1329-30 (claims directed to about 1-3% rhenium and the prior art disclosed range of 0-7% rhenium); *Harris*, 409 F.3d at 1343-44 (claims directed to twelve different elements in a number of ranges and the prior art's disclosure completely encompassed eleven of the twelve ranges and overlapped with the remaining range). Thus, the patentees in those cases attempted to rebut the *prima facie* case of obviousness during patent prosecution when a claimed range overlaps with a prior art range by showing unexpected results. *See Peterson*, 315 F.3d at 1329, 1331.

The *Peterson* patentees failed to show unexpected results across the entire claimed range of 1-3% rhenium; in fact the record actually indicated that there were no unexpected results with 1% and 3% rhenium. *Id.* at 1331. And the *Harris* patentee failed to show the existence of any unexpected result. 409 F.3d at 1343. The holdings of these cases are driven by their specific factual circumstances.

Unlike the patents in *Peterson* and *Harris*, the Moe patents claim something new entirely—low-dose effervescent fentanyl formulations with two particular

excipients, mannitol and SSG—and not narrow ranges that overlap with the prior art. Accordingly, the holdings in *Peterson* and *Harris* do not apply in this case.

Unable to contest the unexpected results, Mylan contends for the first time on appeal that Cephalon never proved that the unexpected pharmacokinetic benefits relate to any novel difference between the claimed invention and the prior art. Mylan has waived this argument because it did not raise it in the district court. *Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1323 (Fed. Cir. 2008) ("It is the general rule that a federal appellate court does not consider an issue not passed upon below.") (citation omitted). Moreover, Mylan mischaracterizes Cephalon's testimony regarding the novelty of the Moe patents. It is the combination of fentanyl, effervescence, mannitol, and SSG that produced the unexpected results. This combination is claimed in the Moe patents. Thus, there is no need to parse out what each member of the combination contributed.

Accordingly, and considering all of the evidence as a whole, the district court's non-obviousness finding should be affirmed.

CONCLUSION

For all the reasons set forth above, the district court's judgment should be affirmed.

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CERTIFICATE OF SERVICE

I certify that on November 6, 2013, true and correct copies of the following:

APPELLEES' RESPONSIVE BRIEF;

CERTIFICATE OF INTEREST; CERTIFICATE OF COMPLIANCE; and

CERTIFICATE OF SERVICE

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CERTIFICATE OF COMPLIANCE

The responsive brief of Appellee Cephalon, Inc. and CIMA Labs, Inc. complies with the type-volume limitation set forth in FRAPP 32(a)(7)(B). The relevant portions of the responsive brief, including all footnotes, contain 13,797 words, as determined by Microsoft Word 2010.

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